

Remarks

Reconsideration of this Application is respectfully requested.

Claim 1 is sought to be amended, claim 14 is sought to be canceled and new claims 15-20 are sought to be added. Support for the amendment to claim 1 and new claims 15-20 can be found, for example, in the specification at page 14, lines 11-19. Upon entry of the foregoing amendment, claims 1-13 and 15-20 are pending in the application, with claim 1 being the independent claim. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Priority

The Examiner acknowledged Applicants' claim for foreign priority based on Argentine Application Nos. 98 01 05611, filed November 6, 1998, and 99 01 00681, filed February 23, 1999, but noted that certified copies of the applications had not been filed as required by 35 U.S.C. § 119(b). (*See* Office Action, page 2.) In accordance with 35 U.S.C. § 119(b)(3) and 37 C.F.R. § 1.55(a)(2), Applicants submit herewith certified copies of the foreign priority applications.

II. Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-3, 6 and 14 under 35 U.S.C. § 102(b) as allegedly being anticipated by Jixian *et al.*, *Bull. Acad. Mil. Med. Sci.* 21:244-246 (1997) (hereinafter "Jixian"). (See Office Action, page 2.) Applicants respectfully traverse this rejection as it may apply to the present claims.

Anticipation of a claim under § 102 can be found only if the prior art reference discloses each and every element as set forth in the claim. See *Glaxo Inc. v. Novopharm Ltd.*, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), *cert denied*, 116 S. Ct. 516 (1995). Further, "[a]n anticipating reference must describe the . . . [claimed] subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention." *ATD Corp. v. Lydall Inc.*, 48 USPQ2d 1321, 1328 (Fed. Cir. 1998). Therefore, in order for the Jixian reference to anticipate the claimed invention, it must describe each and every limitation of Applicants' claimed invention such that the subject matter would be recognized by one skilled in the art. Jixian clearly fails to do so.

Jixian teaches the production of recombinant human erythropoietin using CHO cells in a serum-free medium containing insulin (SFM-p). See Abstract. However, Jixian further teaches that SFM-p comprises DMEM:F12 (1:1) medium and various additives including Se, lipid, vitamins, peptone, transferrin and cytokines. See Abstract. In particular, Jixian teaches that SFM-p contains, in addition to basal medium DMEM:F12, additive A (casein hydrolysate and yeast extract), additive B (Se, ethanolamine and fatty acids) and additive C (insulin, transferrin and growth factors). See Jixian translation, pages 4-5. In contrast to the disclosure of Jixian, the claimed

culture medium does not include, for example, transferrin, yeast extract or casein hydrolysate as additives. Jixian therefore fails to teach the claimed culture medium.

In view of the above, it is clear that Jixian does not disclose each and every element of the claimed subject matter. Therefore, Applicants respectfully request that the rejection of claims 1-3, 6 and 14 under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 4, 5 and 13 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian in view of Koch *et al.*, EP Application No. 0 513 738 A2 (hereinafter "Koch"). (*See* Office Action, page 4.) Applicants respectfully traverse this rejection as it may apply to the present claims.

In order to establish a *prima facie* case of obviousness, the Examiner must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references cited by the Examiner or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings to obtain Applicants' invention. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Second, there must be a reasonable expectation of success. *See In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991.) Third, all the claim limitations must be taught or suggested by the prior art references. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art references, not in Applicants' disclosure. *See In re Vaeck*, 947 F.2d at 491, 20 USPQ2d at 1442 (Fed. Cir. 1991.)

Applicants assert that there is no suggestion or motivation in Jixian or Koch to combine the teachings to obtain Applicants' invention. Moreover, even assuming, *arguendo*, that such a suggestion or motivation to combine the references is present, there would be no expectation of success in generating the claimed invention and all of the claim limitations are not taught or suggested by the references.

As pointed out by Applicants above, Jixian fails to teach a method for obtaining human erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in cell expansion culture medium and culturing the mammalian cells in culture medium consisting of DMEM, F12 medium, insulin and one or more additives selected from the group consisting of NaHCO₃, sugars, ethanolamine, pyruvate, amino acids and mixtures thereof. Koch fails to remedy the deficiencies of Jixian.

Koch teaches production of erythropoietin in a serum-free culture medium containing insulin by cultivating genetically engineered CHO cells. In addition, Koch teaches that, besides insulin, there are other substances that can affect the growth of mammalian cells, such as transferrin. *See* Koch translation at page 2, paragraphs 1 and 2. In order to avoid the use of animal proteins which can be contaminated with pathogenic viruses, Koch employs a water soluble iron compound, such as iron citrate, iron sulfate, iron chloride or potassium hexacyanoferrate, instead of transferrin in the culture medium. A critical aspect of the Koch disclosure is, besides the addition of recombinant insulin from prokaryotes, the addition of a water-soluble iron compound as a transferrin substitute. *See* Koch translation at page 2 and claim 1. Contrary to the Koch disclosure, a water-soluble iron compound to substitute for transferrin in the culture medium (or indeed transferrin itself) is not required in the present invention.

As such, not only does Koch fail to teach all of the limitations of the claimed invention, but in fact teaches a person of ordinary skill in the art that there is not a reasonable expectation of success in producing recombinant EPO without a substitute of transferrin as an extra source of iron.

Obviousness cannot be established by modifying the teachings of the prior art to produce the claimed invention unless there is some teaching, suggestion or motivation to do so found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. *See In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). Based on the disclosures of Jixian and Koch, there is no teaching, suggestion or motivation to use the claimed culture medium comprising insulin. In addition, the mere fact that the Jixian or Koch references could conceivably be modified to make the claimed invention does not render the resultant modification obvious unless the prior art also suggests the desirability of that specific modification. *See In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). The prior art references clearly fail to do so. Accordingly, it is respectfully requested that the rejection of claims 4, 5 and 13 under 35 U.S.C. § 103(a) be withdrawn.

The Examiner further rejected claims 7-10 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian in view of Yanagi *et al.*, *DNA* 8:419-427 (1989) (hereinafter "Yanagi") and Chiba *et al.*, U.S. Patent No. 3,865,801 (hereinafter "Chiba"). (*See Office Action*, page 7.) Applicants traverse this rejection as it may apply to the present claims.

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate, *inter alia*, that all the claim limitations are taught or suggested by the prior art references. *See, e.g. In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As

demonstrated above, Jixian does not teach or suggest the presently claimed invention.

With respect to Yanagi and Chiba, the Examiner asserts that

Yanagi et al[.] teach[] isolation of recombinant human erythropoietin produced by Namalwa cells. Regarding claim[s] 7(c) and 9-10 the cited art teaches separation of EPO containing supernatant from EPO-producing 2A311 cells. The cited art further teaches concentration of EPO from [sic] the cell supernatant. . . . Chiba et al[.] teach[] a method of storing EPO for prolonged periods of time. Regarding claim 7 (d), the cited art teaches storing purified EPO preparation in the frozen state at -20°C.

(Office Action, pages 7-8.) (citations omitted.)

Applicants submit that neither Yanagi nor Chiba remedy the deficiencies of Jixian, in that they, alone or in combination, fail to teach a method for obtaining human erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in cell expansion culture medium and culturing the mammalian cells in culture medium consisting of DMEM, F12 medium, insulin and one or more additives selected from the group consisting of NaHCO₃, sugars, ethanolamine, pyruvate, amino acids and mixtures thereof. Therefore, Applicants submit that the Examiner has failed it establish a *prima facie* case of obviousness with respect to claims 7-10 and respectfully request that this rejection be withdrawn.

Finally, the Examiner rejected claims 7, 11 and 12 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian, Yanagi and Chiba and further in view of van Reis, U.S. Patent No. 5,490,937 (hereinafter "van Reis"). (*See* Office Action, page 9.) Applicants traverse this rejection as well.

As discussed above, the cited art references must teach or suggest all of the claim limitations in order to establish a *prima facie* case of obviousness. Applicants have

demonstrated that neither Jixian, Yanagi nor Chiba teach or suggest the presently claimed invention. Regarding the van Reis reference, the Examiner asserted that

van Reis et al[.] teach[] a tangential flow filtration process and apparatus for separating species of interest (proteins) from a mixture. Regarding claim 11 the cited art teaches a tangential filtration system through filtration membranes having a pore size that separate species of interest having molecular weight of about 1 to 1000kDa. . . . Regarding claim 12, the cited art further teaches filtration through micro porous membranes that has a pore size typically from 0.1 to 10 micrometers, which would inherently sterile [sic] the filtered product.

(Office Action, page 10.) (citations omitted.)

Van Reis is directed to processes for separating compounds of interest from a mixture which comprises subjecting the mixture to tangential flow filtration where the filtration membrane has a specific pore size. Similar to the other cited references, Applicants submit that van Reis does not remedy the deficiencies of Jixian, in that it does not, alone or in combination with Yanagi or Chiba, teach the claimed method. Accordingly, Applicants submit that the Examiner has failed it establish a *prima facie* case of obviousness of claims 7, 11 and 12 and respectfully request that this rejection be withdrawn.

Conclusion

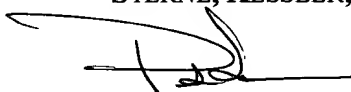
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read 'Peter A. Jackman', is written over a horizontal line.

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